Metabolic control of signaling pathways and metabolic auto-regulation

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KEYWORDS

Cancer metabolism, mass action kinetics, metabolic regulation, post-translational modifications, signaling pathways.

ABBREVIATIONS

AcCoA, acetyl-CoA; AMPK, AMP-activated protein kinase; HIF1α, hypoxia-inducible factor 1-alpha; 4-HNE, 4-hydroxynonenal; IRP1, iron regulatory protein 1; mTOR, mammalian target of rapamycin; MDA, malondialdehyde; NO, nitric oxide; PFK1, phosphofructokinase; PTMs, post-translational modifications; ROS, reactive oxygen species; RNS, reactive nitrogen species; TCA, tricarboxylic acid.

ABSTRACT

Metabolic alterations have emerged as an important hallmark in the development of various diseases. Thus, understanding the complex interplay of metabolism with other cellular processes such as cell signaling is critical to rationally control and modulate cellular physiology. Here, we review in the context of mTOR, AMPK and p53, the orchestrated interplay between metabolism and cellular signaling as well as transcriptional regulation. Moreover, we discuss recent discoveries in auto-regulation of metabolism (*i.e.* how metabolic parameters such as metabolite levels activate or inhibit enzymes and thus metabolic pathways). Finally, we review functional consequences of posttranslational modification on metabolic enzyme abundance and/or activities.

INTRODUCTION

Metabolism is a tightly regulated cellular factory providing essential cellular components such as energy equivalents, redox cofactors, biomass building blocks, and precursors for chemical modifications of proteins or DNA. Hence, metabolism is connected to virtually any cellular process. Consequently, multiple bidirectional feedback and control mechanisms between metabolism and cellular regulation exist to maintain cellular and physiological homeostasis. Aberrant metabolism is thus consequentially and / or causally linked to many diseases including cancer (Vander Heiden et al.

2009; Cantor and Sabatini 2012; Mullen and DeBerardinis 2012; Adam et al. 2014), metabolic syndromes (Kahn et al. 2006; Aroor et al. 2012; Paneni et al. 2014), and neurodegenerative diseases (Kwong et al. 2006; Schapira 2008; Duarte et al. 2014).

Given the emerging importance of aberrant metabolism in many diseases, the question arises, how the fine-tuned balance of metabolic processes is sustained. While top-down regulation of metabolism by signaling and transcription factors is one important aspect, demand and condition-dependent adaption of metabolic homeostasis can only be achieved with a bidirectional feedback system and metabolic auto-regulation (Figure 1). Thus, while signaling and transcription factors regulate metabolism, also metabolic parameters such as metabolites or enzymes regulate the activity of signaling and transcription factors (Figure 1). Moreover, metabolic parameters *per se* auto-regulate metabolism. Such an auto-regulation is either direct (*e.g.* feedback inhibition of an enzyme by the final metabolite product) or indirect (*e.g.* metabolites as precursors for posttranslational modifications of enzymes) (Figure 1).

In this review, we focus first on the metabolic regulation of signaling and transcriptional regulation with the examples of the mammalian target of rapamycin (mTOR), the AMP-activated protein kinase (AMPK) and p53. Second, we discuss recent discoveries in auto-regulation of metabolism, and finally we review the functional consequences of posttranslational modification on metabolic enzyme activities, enzyme abundances, and metabolic pathway regulation.

METABOLIC FEEDBACK TO SIGNALING PATHWAYS AND TRANSCRIPTION FACTORS

Many of the major signaling pathways and downstream transcription factors (which include many tumor suppressors and oncogenes) regulate metabolism. Thus, the complex cell signaling network is able to integrate intracellular and extracellular information, leading to a temporal and spatial balance between anabolic and catabolic processes in order to maintain homeostasis and support growth and proliferation (Gomes and Blenis 2015). However, this regulation over metabolism is not unidirectional but bidirectional, and metabolism also controls signaling pathways.

Metabolite concentrations and to a lesser extent metabolic enzymes are critical regulators in the feedback from metabolism to signaling pathways (Figure 2). Whether metabolic fluxes (metabolite conversion rates) directly regulate signaling pathways has yet to be determined. However, alterations in metabolite concentrations that influence signaling pathways may actually be output components of changes in the flux magnitude. Thus, metabolic fluxes might regulate signaling pathways via metabolite concentrations as a sensory readout. Such a relationship has so far only been described in *E. coli* (Kochanowski et al. 2013), but might occur in mammalian systems as well.

Here, we discuss the feedback regulation that metabolism exhibits on signaling pathways based on three major regulators of cellular metabolism, namely mTOR, AMPK, and p53 (feedback regulation from metabolism to the transcription factor hypoxia-inducible factor 1-alpha (HIF1α) was recently

extensively reviewed (Semenza 2010; Luo and Semenza 2011)) (Figure 2). mTOR, AMPK, and p53 are critically involved in the regulation of cell growth, proliferation, and survival and their connected signaling networks are often altered in pathological states such as cancer. Notably, mTOR, AMPK and p53 activities, as pieces of a larger network, are also interdependent, thus the feedback regulation from metabolism to one of the three might indirectly affect all of them.

Metabolism regulates mTORC1 and mTORC2 activity

The two mTOR complexes C1 and C2 -which are atypical serine/threonine protein kinases- are major regulators of the cellular response to nutrients, growth factors, and stress (Howell and Manning 2011). mTORC1 activity is subject to regulation via various upstream signaling cascades such as LKB1/AMPK (energy stress sensor) or PI3K/AKT (growth factor/insulin signaling) (Ma and Blenis 2009). Many of these upstream signaling cascades converge into the key negative regulator complex TSC1/2 to regulate mTORC1 (Laplante and Sabatini 2012). Critical aspects for the activity of mTORC1 and mTORC2 include interaction with the complex partners raptor and rictor, respectively (Yonezawa et al. 2004; Oh and Jacinto 2011). Moreover, at least for mTORC1, localization at the lysosome is crucial for its activation (Sancak and Sabatini 2009).

Compared to mTORC2, the regulation and function of mTORC1, as a coordinator of the cellular response such as growth, proliferation and survival, has been more extensively characterized (Huang and Fingar 2014). Yet, both complexes regulate cellular metabolism (Polak and Hall 2009), and not surprisingly, metabolic parameters regulate the activity of both complexes. The majority of the known metabolic feedback mechanisms regulating mTOR activity are influenced by metabolite concentration, but metabolic enzymes can also directly control mTOR activity.

Amino acid concentrations regulate mTORC1 activity

Extracellular amino acids including leucine, arginine, and serine activate mTORC1 activity (Blommaart et al. 1995; Hara et al. 1998; Wang et al. 1998; Ye et al. 2012; Maddocks et al. 2013). Additionally, mTOR is also indirectly regulated by glutamine, as discussed below (Nicklin et al. 2009; Vivanco 2014). Yet, the extent to which intracellular amino acid concentrations are directly linked to mTORC1 activity, and the mechanism by which the concentration of specific amino acids are sensed, remains largely unknown. However, for some amino acids (and also other metabolites) the mechanisms on how they modulate mTORC1 activity become increasingly revealed.

Recently the mechanism by which arginine activates mTORC1 activity has been investigated. Thereby, it was found that intra-lysosomal availability of arginine can be sensed by SLC38A9, a novel lysosomal transmembrane protein that interacts with the Rag GTPases and regulator (Rebsamen et al. 2015; Wang et al. 2015) (Figure 2).

Leucine, which is an essential amino acid that is taken up by the cell, supports the recruitment of mTORC1 to the lysosome (Laplante and Sabatini 2012; Jewell et al. 2013) (Figure 2). Interestingly, the ability of leucine to stimulate mTORC1 activity goes beyond an on-off mechanism. Variations in intracellular leucine concentrations are directly translated into alterations in mTORC1 activity. This was demonstrated in cells lacking the enzyme branched chain aminotransferase, which degrades branched chain amino acids including leucine. Loss of branched chain aminotransferase consequently led to increased intracellular leucine concentrations and accordingly increased mTORC1 activity (She et al. 2007; Ananieva et al. 2014). Although the full mechanism by which leucine stimulates the recruitment of mTORC1 to the lysosome is not fully understood, it is possible that the positive effect of leucine on mTORC1 activity depends on the presence of leucyl-tRNA synthase (Han et al. 2012) and/or the vacuolar H^+-ATPase (Zoncu et al. 2011). Thereby, both factors may be needed for the leucine-induced activation of the Rag GTPases, which consequently will lead to the recruitment of mTORC1 to the lysosome (Laplante and Sabatini 2012; Jewell et al. 2013; Ramsdell and Gulland 2014).

Interestingly, the ability of leucine to stimulate mTORC1 activity may also depend on the intracellular availability of the non-essential amino acid glutamine (Figure 2). It has been shown that transport of extracellular leucine into the cell (where it will lead to the recruitment of mTORC1 to the lysosome) only occurs when glutamine is simultaneously exported from the cell (Nicklin et al. 2009). Particularly, some cancer cells have acquired the ability to sustain elevated concentrations of intracellular glutamine, which consequently can prime these cells for increased mTORC1 activity (Nicklin et al. 2009). The importance of glutamine metabolism for mTORC1 activity outreaches the function as counter-amino acid import of leucine (Figure 2). Recently, Jewell et *al.* demonstrated that glutamine itself stimulates mTORC1 activation at the lysosome via Arf1-GTPase in a RagA and RagB-independent manner (Jewell et al. 2015).

α-ketoglutarate concentrations regulate mTORC1 activity

Glutamine can be an important carbon source for the production of the tricarboxylic acid (TCA) cycle metabolite α-ketoglutarate, and a significant number of cancer cells are addicted to glutamine (Vivanco 2014). Like leucine, the intracellular availability of α-ketoglutarate (but not the TCA cycle metabolite malate) was shown to activate Rag-GTPases, thus leading to mTORC1 recruitment to the lysosome and increased activity (Duran et al. 2012; Marino et al. 2014) (Figure 2). Moreover, α-ketoglutarate can impact mTORC1 activity by fueling acetyl-CoA (AcCoA) production, which subsequently can lead to mTORC1 activation via an acetyltransferase EP300-dependent mechanism (Marino et al. 2014). Consequently, not only changes in α-ketoglutarate concentrations but any alteration that leads to decreased AcCoA levels (*e.g.* such as inhibition of the mitochondrial pyruvate carrier (Marino et al. 2014)) can decrease mTORC1 activity.

Yet, α-ketoglutarate-dependent regulation of mTORC1 activity is not fully understood. Controversially, it has been described that increased α-ketoglutarate concentrations can also lead to decreased mTORC1 activity. Shanware *et al.* (Shanware et al. 2014) demonstrated that glutamine deprivation induced mTORC1-JNK dependent chemokine secretion is inhibited when cell permeable α-ketoglutarate is provided in the cell culture media. Accordingly, Chin *et al*. (Chin et al. 2014) showed in *C. elegans* (and for some key experiments also in mammalian cells) that α-ketoglutarate inhibited the ATP synthase, which consequently led to decreased ATP levels and subsequently decreased mTORC1 activity.

Thus, α-ketoglutarate alterations can lead to either mTORC1 activation or inhibition and it is not revealed yet which aspects determine the functional consequences of α-ketoglutarate concentration perturbations on mTORC1 activity.

ATP concentrations regulate mTORC1 activity

Several mechanisms have been described for how a drop in ATP levels reduces mTORC1 activity (Kim et al. 2013b) (Figure 2). Dennis *et al.* (2001) proposed mTORC1 as a direct sensor of intracellular ATP due to its high K_m for ATP (around 1mM) (Dennis et al. 2001). In agreement with this idea, Kim *et al*. (Kim et al. 2013c) have shown that decreased ATP levels led – independent of AMPK – to the disassembly of the ATPase containing TTT-RUVBL1/2 complex. The functional TTT-RUVBL complex is required for the assembly and/or stability of PIKK family kinases such as mTORC1, and for its subsequent recruitment and activation at the lysosome (Kim et al. 2013c).

Moreover, several groups have found that mTORC1 also indirectly senses low energy through multiple AMPK-dependent mechanisms (Figure 2). Under energy stress, AMPK is activated and inhibits mTORC1 through direct phosphorylation of TSC2 at Ser1345, likely leading to the activation of its GAP activity and thus inactivation of Rheb (Inoki et al. 2003). Additionally, the priming phosphorylation of TSC2 by AMPK is necessary for the subsequent phosphorylation and activation of TSC2 by GSK3 at Ser1337/1341, downstream of the Wnt pathway (Inoki et al. 2006). AMPK also inhibits mTORC1 in a TSC-independent manner by directly phosphorylating Raptor at Ser722/792, leading to the association of Raptor with 14-3-3 (Gwinn et al. 2010).

Thus, ATP can directly or indirectly (via AMPK) influence mTORC1 activity and thus links the cellular energy status to nutrient signaling.

Fatty acids regulate mTORC1 and mTORC2 activity

Fatty acids have also been discovered to be regulators of mTORC1 and mTORC2 activity (Figure 2). Specifically, n-3 polyunsaturated fatty acids, which have been associated with decreased cancer risk (Butera et al. 1992), have been proposed to inhibit both mTORC1 and mTORC2 activity (Liang et al. 2013). Thereby, the mechanism by which n-3 polyunsaturated fatty acids control mTORC1 or mTORC2 activity is largely unknown. Yet, at least for mTORC1, there is evidence that neither AMPK

nor TCS2 is required for this inhibition, but that the mTORC1-raptor interaction might be involved (Liang et al. 2013).

Moreover, cis-vaccenic acid (18:1, n-7) -the unsaturated elongation product of palmitoleic acid (16:1,n-7), which is produced by fatty acid elongase 5- seems to promote mTORC2 activity (Tripathy and Jump 2013). Mechanistically, it has been proposed that increased fatty acid elongase 5 and subsequently increased cis-vaccenic acid levels induce rictor expression and mTORC2-rictor interaction (Tripathy and Jump 2013).

Similarly, phosphatidic acid, the product of phosphatidylcholine hydrolysis by phospholipase D in response to mitogens, has been proposed to be required for mTORC1 activation. Phosphatidic acid has been proposed to compete with rapamycin to interact with the FK506 binding protein12 domain of mTORC1 (Fang et al. 2001). Interestingly, increased phospholipase D activity has been implicated with increased survival and rapamycin resistance of breast cancer cell lines (Chen et al. 2003; Chen et al. 2005).

Metabolic enzymes regulate mTORC1 activity

mTORC1 activity directly relates to nutrient availability, which does not only include amino acids but also sugar carbon sources such as glucose. Thus, integrating glucose metabolism with mTORC1 activity is critical for cellular proliferation and survival. Roberts *et al.* discovered that upon glucose deprivation or decrease of its product glucose-6-phosphate, hexokinase 2 - an enzyme of upper glycolysis - binds and inhibits mTORC1 (Roberts et al. 2014) (Figure 2). This interaction between mTORC1 and hexokinase 2 consequently led to increased autophagy. Notably, this regulation of mTORC1 by hexokinase was only observed for isoform 2, which is expressed among other tissues also in a significant number of tumors (Shinohara et al. 1994; Wolf et al. 2011). Thus, cancer cells might anticipate the switch to hexokinase isoform 2 to avoid nutrient depletion induced cell death by inducing mTORC1 dependent autophagy.

In conclusion, these findings support a key role of mTORC1 and C2 as sensors of the metabolic state of the cell and their coordinating role in linking nutrient metabolism and growth signaling. It is expected that future work will lead to discoveries of additional metabolites, enzymes, and potentially metabolic fluxes that regulate mTORC1 and C2 activity and thus allow a fine-tuned, temporal, spatial, and condition-dependent activation profile of mTORC1 and C2.

Metabolism regulates AMPK activity

AMPK is an AMP-sensitive protein kinase, which constitutes the major energy stress sensor in the cell (Hardie et al. 2012; Shirwany and Zou 2014). As an energy sensor, AMPK phosphorylation and thus activation is sensitive to AMP concentration and/or AMP:ATP ratio (Carling et al. 1989; Chen et al. 2012; Gowans et al. 2013; Hardie 2014). AMPK activation can lead to various cellular responses

concerning cellular proliferation, catabolism/anabolism switches, cell survival or apoptosis (Hardie et al. 2012; Shirwany and Zou 2014). Thus, any change in cellular metabolism resulting in altered AMP concentration and/or AMP:ATP ratio might modulate AMPK activity (Hardie et al. 2012; Shirwany and Zou 2014) (Figure 2). Examples for energy stress induction and consequently AMPK activating events include the inhibition of complex I of the electron transport chain (Hinke et al. 2007; Ota et al. 2009), inhibition of fumarate hydratase (Tong et al. 2011; Bardella et al. 2012), or more unexpected metabolic alterations such as serine starvation (Maddocks et al. 2013).

Notably, differences between long- and short-term energy stresses can have differential effects on AMPK activation. As such it was shown that inhibiting complex II of the respiratory chain using the drug TTFA resulted on a short-term perspective in increased AMPK phosphorylation and thus activation, via an increase in the AMP:ATP ratio (Tong et al. 2011). However, long-term treatment with TTFA resulted overall in decreased AMPK levels (Tong et al. 2011). Similarly, differential responses in AMPK activity upon fumarate hydratase deletions have been observed (Tong et al. 2011; Bardella et al. 2012), which implies further variations in the energy stress response based on the overall genetic landscape of cells and specifically tumor cells.

In addition to energy stress, AMPK can also be activated by reactive oxygen species (ROS), nitric oxide (NO) and reactive nitrogen species (RNS) generated by metabolism (Cardaci et al. 2012; Chang et al. 2015) (Figure 2). While many metabolic reactions such as the electron transport chain and urea cycle can generate ROS and NO, respectively, the inhibition of metabolic processes responsible for redox balancing can also contribute to increase oxidative stress (Sabharwal and Schumacker 2014). One striking example illustrating this, is the inverse activity relationship between malic enzyme mitochondrial isoform 2 expression and AMPK activation (Jiang et al. 2013). Malic enzyme 2 can recover oxidized $NADP^+$ to reduced NADPH. Hence, the latter can be used for ROS scavenging. Consequently, malic enzyme 2 knockdown increases reactive oxygen species, which in turn induce AMPK activation (Jiang et al. 2013). Notably, beyond AMPK signaling, ROS can in general activate various signaling cascades and transcription factors, such as PI3K/AKT, MAPK/ERK, HIF1α, NRF2 and NFκB, (Li et al. 2013; Sabharwal and Schumacker 2014; Reczek and Chandel 2015).

Attributing to its role as energy sensor many of the known metabolic signals regulating AMPK activity converge at the level of the energy equivalents ATP/AMP. Additionally, AMPK activity is highly dependent on other signaling components such as mTORC1, LKB1, or CaMKKβ (Wang and Guan 2009; Mihaylova and Shaw 2011).

Metabolism regulates p53 activity

p53 is an important tumor suppressor in cells (Green and Kroemer 2009) and functions as a regulator of cell cycle arrest, senescence, apoptosis, and cellular metabolism (Green and Kroemer 2009; Vousden and Ryan 2009; Berkers et al. 2013). Strikingly, it has been shown that p53-

dependent regulation of cellular metabolism can be sufficient -at least in mice- to inhibit tumor formation (Chaneton et al. 2012). While we have extensive knowledge about the regulation p53 exhibits on cellular metabolism (Vousden and Ryan 2009; Puzio-Kuter 2011; Berkers et al. 2013), there is also recent evidences for a feedback control from metabolism to p53 (Figure 2).

Indirectly, p53 activity is linked to metabolism via AMPK signaling (Jones et al. 2005) (Figure 2). Activation of AMPK leads to an increase of p53 transcription, direct phosphorylation, and stabilization of p53 (Jones et al. 2005; Okoshi et al. 2008). Examples for such are the activation of p53 via AMPK upon malic enzyme 2 knockout (Jiang et al. 2013). Moreover, serine starvation also has been shown to activate p53 (Maddocks et al. 2013), potentially via AMPK activation or a ribonucleotide depletion-dependent mechanism (Linke et al. 1996).

However, an AMPK-independent activation of p53 via metabolism has also been revealed (Figure 2). An increase in ADP concentrations can directly promote the binding of p53 to DNA, while it has been described that high ATP concentrations rather dissociates p53 from DNA (Okorokov and Milner 1999). p53 as a master regulator of pro-oxidant and anti-oxidant responses can also be activated by ROS, leading to a feed-forward regulation loop (Liu et al. 2008). Moreover, NAD^+ levels (but also AMPK) can influence p53 activity via sirtuin 1 (SIRT1). Thereby, SIRT1 has been shown to deacetylate and inactivate p53 (Vaziri et al. 2001; Yi and Luo 2010; Lee et al. 2012; Lau et al. 2014).

Additionally, at least two metabolic enzymes can regulate p53 activity. Jiang *et al*. discovered that upon knockdown of the cytosolic malic enzyme isoform 1, the E3 ubiquitin-protein ligase MDM2-mediated degradation of p53 decreased (Jiang et al. 2013) (Figure 2). Specifically, malic enzyme 1 knockdown led to decreased expression of MDM2 and subsequently increased protein levels of p53. How malic enzyme 1 alters MDM2 expression still needs to be determined. Additionally, it has been revealed that cytosolic malate dehydrogenase 1 increases p53 activity upon glucose deprivation (Lee et al. 2009) (Figure 2). Malate dehydrogenase 1 can directly bind to p53 and thereby acts in the nucleus as transcriptional coactivator of p53 dependent transcription.

In conclusion, the feedback regulation of p53 by metabolism occurs at several levels both directly and indirectly. Which mechanism (*i.e.* direct or indirect regulation) of this metabolic regulation of p53 is the most important one, remains to be determined. Given the role of p53 in keeping cellular homeostasis, it can be expected that in the future more feedback mechanisms from metabolism to p53 will be discovered.

Here, we have reviewed how three major cellular regulators are controlled by metabolism. While it has been known for a long time that signaling pathways regulate metabolism, this new nature of a bidirectional feedback between metabolism and signaling allows a mechanistic understanding of cellular physiology. Although many links between metabolism and signaling still need to be unraveled, already the next challenge arises, namely to bring our understanding to a level that allows

us to control cellular physiology through targeted modulations of the signaling – metabolism interplay.

METABOLIC AUTO-REGULATION

Metabolism is a biochemical reaction network, in which nutrients are converted to produce energy, biomass building blocks, and cofactors. The utilization of the metabolic network is coupled to the demands of its products, which is supported by the fact that nutrient uptake rates have been found to correlate with cell size and protein synthesis under non-stressed conditions (Dolfi et al. 2013). To meet and coordinate these demands, cellular metabolism requires a highly responsive, quickly adaptable and fine-tuned regulation. This can be achieved by metabolic auto-regulation (*e.g.* competitive inhibition or allosteric interactions), where metabolism is modulated by its own products, *i.e.* metabolites (summarized in (Michal and Schomburg 2013)). The most classical auto-regulation of metabolism is feedback inhibition, where a product of a biochemical pathway inhibits early enzymatic steps in the same pathway to prevent overproduction of the final product. Yet, metabolic pathways could also be inhibited by metabolites of other pathways, as exemplified with the Randle cycle, where citrate inhibits phosphofructokinase (PFK1) (Denton and Randle 1966), or with AcCoA regulation of PFK1 (Jenkins et al. 2011; Michal and Schomburg 2013). Additionally, metabolic pathways could be regulated by means of feed-forward activation, such as pyruvate kinase M2 activation via fructose-1,6-bisphosphate (summarized in (Michal and Schomburg 2013)). Overall, intra-metabolic feedback regulation allows the cell to flexibly adapt its metabolism to a particular intra- or extracellular condition on a short time-scale (Poorman et al. 1984; Jenkins et al. 2011). This flexibility is further demonstrated in studies where the inhibition of ATP production via fermentation subsequently leads to oxidative ATP production via respiration and vice versa (Sanchez-Cenizo et al. 2010; Jose et al. 2011; Billiard et al. 2013; Fendt et al. 2013a; Doherty et al. 2014). Given these prominent examples of metabolic auto-regulation, we will focus here on recently discovered and unexpected regulation that metabolic enzymes or metabolite concentrations impose on the activity of metabolic pathways (Figure 3).

Metabolic regulation of glycolysis and connected (biosynthetic) pathways

Although some cells can grow without glucose (Reitzer et al. 1979; Wice et al. 1981; Linker et al. 1985; Niitsu et al. 1999) and some tissues such as the liver are even optimized to produce glucose via gluconeogenesis (Nordlie et al. 1999), many tumor cells (Czernin and Phelps 2002) but also non-transformed cells such as endothelial cells (De Bock et al. 2013) exhibit high glycolytic rates and lactate excretion. Glycolytic rates can be coupled to oxygen availability, which is known as the Pasteur effect, or be independent of oxygen, which is referred to as aerobic glycolysis (Diaz-Ruiz et al. 2011; Lunt and Vander Heiden 2011; Dell' Antone 2012). Aerobic glycolysis can be further divided into the Crabtree effect and the Warburg effect (Diaz-Ruiz et al. 2011; Dell' Antone 2012). The

Crabtree effect relates to extracellular glucose concentrations and hence reversible glucose repression, whereas the cause for the Warburg effect remains controversial (Diaz-Ruiz et al. 2011; Lunt and Vander Heiden 2011; Dell' Antone 2012).

Glycolysis and its connected pathways, such as the pentose phosphate pathway or the serine biosynthesis pathway can further provide energy (ATP via glycolysis), redox co-factors ($NAD(P)^+$ / NAD(P)H via pentose phosphate pathway, pyruvate fermentation, or serine-folate metabolism (Lewis et al. 2014; Ye et al. 2014)), and precursors for posttranslational modifications such as glycosylations or acetylations (Wellen et al. 2009; Metallo and Vander Heiden 2010; Wellen et al. 2010; Jozwiak et al. 2014; Xu et al. 2014a). The balance between ATP, redox, and biomass building blocks producing pathways is partially coordinated via intra-metabolic feedback mechanisms and important to maintain metabolic homeostasis: Hitosugi *et al.* discovered that 3- and 2-phosphoglycerate, which are interconverted by phosphoglycerate mutase 1, critically link glycolysis with the pentose phosphate pathway and serine biosynthesis (Hitosugi et al. 2012) (Figure 3). Specifically, accumulation of 3-phosphogycerate, which occurs upon phosphoglycerate mutase 1 inhibition or knockdown (Fendt et al. 2010; Hitosugi et al. 2012), inhibits the pentose phosphate pathway enzyme 6-phosphogluconate dehydrogenase (Hitosugi et al. 2012) (Figure 3). Thus, inhibition of lower glycolysis will result in a coordinated downregulation of the pentose phosphate pathway activity. Additionally, 2-phosphoglycerate, the product of phosphoglycerate mutase 1, activates the serine biosynthesis pathway enzyme 3-phosphoglycerate dehydrogenase, which uses 3-phosphoglycerate as a substrate (Hitosugi et al. 2012) (Figure 3). Consequently, glycolysis, the pentose phosphate pathway and serine biosynthesis can be coordinated via the activity of phosphoglycerate mutase 1. Strikingly, many cancer cells display increased phosphoglycerate mutase 1 activity and expression (Corcoran et al. 2006; Roberts et al. 2010; Hitosugi et al. 2012), potentially to orchestrate their metabolic demands for uncontrolled proliferation.

Interestingly, regulation between the serine biosynthesis pathway and glycolysis is bidirectional. It has been discovered that serine can act as an allosteric activator of pyruvate kinase M2 (Chaneton et al. 2012) (Figure 3). Thus, low serine levels lead to a decreased pyruvate kinase M2 activity and consequently to a build-up of upper glycolytic intermediates. This, in turn, will provide increased substrate concentrations for biosynthetic pathways that branch off glycolysis (Lunt and Vander Heiden 2011; Lunt et al. 2015). In addition, pyruvate kinase M2 activity is also inhibited by ROS, which allows cancer cells to counteract oxidative stress by increasing their reducing potential via the oxidative pentose phosphate pathway (Anastasiou et al. 2011). Therefore, allosteric coupling of pyruvate kinase 2 activity to other metabolic pathways allows the cell to adequately adapt to the different physiological states (Gui et al. 2013). In contrast to pyruvate kinase M2, pyruvate kinase M1 is constitutively active (Ikeda et al. 1997). Moreover, pyruvate kinase M1 expression is anti-correlated with proliferation (Israelsen et al. 2013) and has recently been found to impair *de novo*

nucleotide biosynthesis (Lunt et al. 2015). Thereby, pyruvate kinase M1 expression is dominant over pyruvate kinase M2 (Lunt et al. 2015). In sum, these findings provide a mechanistic understanding why many proliferating cells, including many cancer cells express pyruvate kinase M2 rather than pyruvate kinase M1.

Redox control of the pyruvate branch-point

Pyruvate can be seen as one of the major intersection metabolites between glycolysis and the TCA cycle, because it can *i)* be fermented to lactate, *ii)* be transaminated to alanine, *iii)* fuel the oxidative TCA cycle via AcCoA, or *iv)* contribute to TCA cycle anaplerosis via oxaloacetate. The TCA cycle is further coupled to respiration, as it reduces the redox equivalent NAD^+ to NADH, which is utilized by electron transport chain. Alterations in the electron transport chain activity have been shown to impact pyruvate entry into the TCA cycle via pyruvate dehydrogenase (Fendt et al. 2013b) (Figure 3). Specifically, upon electron transport chain inhibition, the NAD^+/NADH ratio decreases (Fendt et al. 2013b; Karamanlidis et al. 2013; Mullen et al. 2014) and subsequently the flux through the pyruvate dehydrogenase reaction decreases, since it needs NAD^+ as a cofactor substrate (Fendt et al. 2013b). Thus, the NAD^+/NADH ratio can regulate based on mass action whether pyruvate is oxidized via AcCoA or used for fermentation. Hence, mass action kinetics can be powerful control mechanisms to shunt metabolites into different metabolic pathways.

Metabolic regulation of glutamine metabolism

Similar to the fate of pyruvate, the fate of glutamine when entering the TCA cycle via α-ketoglutarate can be determined by mass action (Figure 3). α-ketoglutarate is either oxidized to succinate or reduced to citrate. A low $NADP^+$/NADPH ratio (Gameiro et al. 2013a; Mullen et al. 2014) and a high α-ketoglutarate/citrate ratio (Fendt et al. 2013b; Gameiro et al. 2013b) promote the reductive carboxylation of α-ketoglutarate to citrate. Notably, the interplay between the NADH producing succinyl-CoA synthase and the nicotinamide nucleotide transhydrogenase can provide sufficient amounts of NADPH to promote reductive glutamine metabolism (Gameiro et al. 2013a; Mullen et al. 2014).

Glutamine and glutamate metabolism are further coordinated with fatty acid metabolism and leucine uptake (Fahien and Kmiotek 1981; Tomita et al. 2011; Son et al. 2012) (Figure 3). Specifically, high palmitoyl-CoA concentrations lead to the inhibition of glutamate dehydrogenase (Fahien and Kmiotek 1981; Son et al. 2012) and thus might allow balancing carbon entry into the TCA cycle between glutamine and β-oxidation. In contrast, leucine activates glutamate dehydrogenase (Tomita et al. 2011) and might constitute one possibility to balance intracellular nitrogen-metabolism.

Regulation of the TCA cycle and respiration by nitric oxide

Another metabolic regulator is the urea cycle product NO, which can regulate respiration and the TCA cycle either directly or indirectly via S-nitrosation or tyrosine nitration (Chang et al. 2015). For example, NO reversibly inhibits cytochrome c oxidase (complex IV) by interacting with the heme iron or with the oxidized copper in the heme iron:copper center (Schweizer and Richter 1994; Mason et al. 2006). In addition, high concentrations of NO lead to an irreversible inhibition of cytochrome c oxidase via S-nitrosation of the cysteine residues (Zhang et al. 2005). Besides complex IV also complex I and complex III are reported targets of NO in the electron transport chain. Within the TCA cycle, NO inhibits aconitase and the $NADP^+$-dependent isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase (Chang et al. 2015). Given the redox-control of pyruvate and glutamine metabolism, which we discussed in the section 'redox-control of the pyruvate branch-point', NO might have a crucial role in the coordination of these processes.

Metabolic regulation of lipid metabolism by TCA cycle metabolites

Finally, TCA cycle metabolites can regulate lipid metabolism (Figure 3). While it has been known for decades that citrate (and other metabolites) activates fatty acid synthesis through allosteric regulation of acetyl-CoA carboxylase (summarized in (Michal and Schomburg 2013)), it has been discovered in recent years that succinate can inhibit lipolysis in white adipose tissue (Regard et al. 2008). Specifically, succinate activates the succinate receptor (G protein-coupled receptor 91), which inhibits adenylate cyclase and thus cAMP formation (Sundstrom et al. 2013). Subsequently, inhibition of protein kinase A by reduced cAMP levels results in decreased activity of lipases. The importance of succinate for the inhibition of lipolysis beyond white adipose tissue remains to be determined, but the wide expression of the succinate receptor (Deen and Robben 2011) could implicate a further importance of succinate as a regulator of lipolysis.

Here we reviewed the most recent insights about metabolic auto-regulation. The intra-metabolic interactions constitute an intertwined network, where metabolites and enzymes directly regulate the activity of their own pathway, as well as the activity of more remote pathways (*e.g.* the inhibition of *de novo* nucleotide metabolism by pyruvate kinase M1). Yet, the *in vivo* relevance of the various possible metabolite-enzyme-interactions is so far unexplored, and more systematic methods as suggested by Link *et al.,* 2013 (Link et al. 2013) might help in their quantification. Moreover, the regulatory interactions between enzymes and metabolites might be combined with our knowledge on synthetic lethality (Folger et al. 2011). This might further allow a rational design of more specific combinatorial therapies to constrain cancer progression, as it was recently shown by Gameiro *et al.,* who combined a knockdown of mitochondrial nucleotide transhydrogenase with glucose deprivation to prevent carbon entry into the TCA cycle (Gameiro et al. 2013a) or by Fendt *et al*., who combined

metformin treatment with the inhibition of glutamine metabolism to reduce *de novo* fatty acid biosynthesis (Fendt et al. 2013a).

REGULATION OF METABOLISM BY POSTTRANSLATIONAL MODIFICATIONS

Posttranslational modifications (PTMs) are chemical modifications of protein residues through covalent additions of functional groups. PTMs can be classified into reversible (glycosylation, palmitoylation, poly-ADP ribosylation, phosphorylation, succinylation, methylation, acetylation, ubiquitination, carboxylation, thiolation (nitrosylation, glutathionylation), hydroxylation) or irreversible (succination, prenylation, myristoylation, proteolysis, isopeptide bond formation) modifications (Walsh et al. 2005). Reversible PTMs are more prone to offer a dynamic modulation of protein activity in response to environmental and internal signals, while irreversible PTMs are mostly, but not exclusively, associated with protein synthesis and degradation, membrane targeting, and protein-protein interaction (Walsh et al. 2005).

Thereby, central carbon metabolism provides the precursors necessary for the addition of PTMs to proteins, but also for DNA modifications. Histone and DNA modifications (mainly methylation) lead to major epigenetic changes and this type of metabolism-dependent regulation has been already extensively reviewed (Gut and Verdin 2013; Kaelin and McKnight 2013; Carrer and Wellen 2014). Yet, metabolic enzymes are themselves targets of PTMs, leading to a feedback regulation of metabolism. Here we provide various examples depicting how metabolism regulates itself through PTMs (Figure 4).

PTMs that are largely independent of metabolite substrates

Two of the most universally and extensively used PTMs to regulate protein activity and abundance are phosphorylation and ubiquitination, respectively.

Regulation via phosphorylation, depends mainly on the activity of kinases and their counteracting phosphatases (Newman et al. 2014). Although ATP is the necessary co-factor of phosphorylation modifications, ATP concentrations are not limiting under physiological conditions.

Ubiquitination consists in the addition of monomeric or polymeric chains of the ubiquitin protein to a targeted protein for degradation by the proteasome (Komander and Rape 2012). Ubiquitin homeostasis is the result of a fine balance between ubiquitin synthesis, degradation by the proteasome, and usage/recovery of ubiquitin pools by the ubiquitinating and deubiquitinating enzymes, which leads to adequate levels of ubiquitin under physiological conditions (Kimura and Tanaka 2010). Hence, like phosphorylation, ubiquitination depends mainly on the activity of the ubiquitin system enzymes (ubiquitin-activating E1, ubiquitin-conjugating E2, and ubiquitin ligase E3 enzymes) and their counteracting deubiquitinating enzymes. A supplementary auto-regulation layer of ubiquitination comes from the ubiquitination/deubiquitination of ubiquitin ligases E3 themselves (de Bie and Ciechanover 2011).

Interestingly, while the ubiquitin–proteasome system is responsible for the degradation of proteins and *de facto* of metabolic enzymes, the proteasome is an ATP-dependent and ROS-sensitive system, which is in turn regulated by metabolism via PTMs (Livnat-Levanon and Glickman 2011; Sledz et al. 2013). Specifically, the proteasome is regulated by PKA-mediated phosphorylation and by O-GlcNAcylation and hence glucose metabolism (Zhang et al. 2003; Zhang et al. 2007; Ruan et al. 2013).

PTMs that are dependent on metabolite substrates

Conversely, other PTMs such as acetylation, succinylation, malonylation or ADP-ribosylation events depend on the availability of the metabolite substrates AcCoA, succinyl-CoA, malonyl-CoA or ADP-ribose (from NAD^+), respectively (Alderson et al. 2006; Peng et al. 2011; Zhang et al. 2011; Lee et al. 2014). PTMs do not only depend on concentrations of these substrates but also on the localization of these pools of substrates. Specifically, relative concentrations of AcCoA, succinyl-CoA and malonyl-CoA between cytosol and mitochondria can directly affect the nature and abundance of the related PTMs between these compartments (Newman et al. 2012). This compartmentalization of PTMs might participate in the coupled regulation of glycolysis, glucose oxidation and fatty acid oxidation (Newman et al. 2012).

Acetylation, ribosylation, malonylation, succinylation and succination

The substrate-dependent modifications can be regulated by specific transferases and sirtuins. For example, acetyltransferases and sirtuins are counterparts in acetylating and de-acetylating proteins (Choudhary et al. 2014). Notably, the different sirtuins (which have specificities for acetylation, succinylation, malonylation, but also ADP-ribosylation) depend on the availability of NAD^+ (Sauve and Youn 2012). Thus, changes in the redox cofactor ratio will affect their activity. Additionally, it has been reported that depending on intracellular pH and the metabolite substrate concentrations, spontaneous acetylations and succinylations of mitochondrial proteins can occur (Wagner and Payne 2013). Similarly, besides sirtuin 4 mediated ADP-ribosylation (Haigis et al. 2006) endogenous ADP-ribosylation can be induced non-enzymatically by nitric oxide (Dimmeler et al. 1992; Molina y Vedia et al. 1992; Zhang and Snyder 1992).

Importantly, unlike acetylation and succinylation, succination is an irreversible and spontaneous event, which is driven by high fumarate concentrations (Alderson et al. 2006). Yang *et al.* (Yang et al. 2014) found that succination mainly occurs in redox regulating enzymes at their cysteine residues. Therefore, targets of succination might be identified based on their chemical properties.

Oxidative PTMs

Oxidative PTMs are dependent on reactive oxygen, nitrogen and chlorine species levels, which are constitutive by-products of cellular metabolism and can be considered as signaling molecules (Reczek and Chandel 2015). Amino acids that are targeted by these PTMs in proteins are free

cysteine, methionine, tyrosine, and tryptophan residues. The specific chemical oxidative modifications on these residues have been well reviewed elsewhere (Ryan et al. 2014).

One of the most occurring oxidative PTM is glutathionylation, which leads to the reversible creation of a disulfide bond between the free thiol of cysteines and reduced glutathione. Protein glutathionylation can be non-enzymatically-driven when the ratio of reduced glutathione to oxidized glutathione is around 1 during oxidative stress, or enzymatically-driven by glutaredoxin-1 and 2 (Mannervik and Axelsson 1980; Gallogly et al. 2009). This provides an important role for protection of thiol groups, and often occurs in proteins that are prone to oxidative stress and particularly in mitochondrial metabolic enzymes (Nulton-Persson et al. 2003; Mailloux and Willmore 2014). Corroborating this notion, complex I possesses several glutathionylation sites, notably on Cys531 and Cys704 on the Ndusf1 subunit. These cysteine residues are close to the NADH binding site and their modification lowers complex I activity and possibly induces a conformational change that protects NADH from oxidation (Hurd et al. 2008).

Secondary products of lipid (acrolein, 4-hydroxynonenal (4-HNE), malondialdehyde (MDA)) and glucose oxidation (glyoxal, methylglyoxal) by reactive species can further lead to a non-enzymatically-driven irreversible oxidation of cysteine, lysine, arginine and histidine residues and result in protein carbonylation (Curtis et al. 2012). Carbonylation of proteins impairs their functions, lead to their degradation by the proteasome or their toxic aggregation (Curtis et al. 2012). Since the targets of carbonylation depend on the oxidative environment of the cell, abundance, and proximity to reactive species, numerous mitochondrial metabolic enzymes are subject of carbonylation (Curtis et al. 2012). For example, complex I of the electron transport chain was shown to be carbonylated at residue Arg76, close to the catalytic site, leading to a significant decrease of its activity (Ryan et al. 2012).

Metabolic enzymes can be subject to more than one oxidative PTM, with a major incidence on metabolic control. For example, there are two isoforms of aconitase, one cytosolic and one mitochondrial. Aconitase activity is regulated among other PTMs by reversible oxidation of $[4Fe\text{-}4S]^{2+}$ cluster, oxidation of cysteine, tyrosine and tryptophan residues and carbonylation. The oxidized form of cytosolic aconitase is involved in the control of iron homeostasis as iron regulatory protein 1 (IRP1), while the oxidation of mitochondrial aconitase might limit the production of intermediates of the TCA cycle and subsequently generation of ATP and ROS (Lushchak et al. 2014). Alpha-ketoglutarate dehydrogenase, as a rate limiting enzyme of the TCA cycle, has also been proposed as an important mitochondrial redox sensor, since its activity is majorly impacted by glutathionylation and carbonylation of its cofactor lipoic acid (McLain et al. 2011).

Glycosylations

Finally, proteins can be modified by glycosylations. There are N-linked and O-linked glycosylations, as well as O-GlcNAcylation (Denzel and Antebi 2014). All glycosylations involve the hexosamine

pathway, and its product UDP-GlcNAc (Denzel and Antebi 2014). The hexosamine pathway branches off glycolysis at fructose-6-phosphate and it is likely that the glucose uptake rate is a limiting factor for UDP-GlcNAc production and further glycosylation. Specifically, Kawauchi *et al*., found that IKKβ O-GlcNAcylation depends on the glucose uptake rate (Kawauchi et al. 2009). Corroborating these results, Wellen *et al*., 2010 has shown that low glucose uptake rates provoked a decrease in IL-3 receptor surface expression and that this could be re-established by supplementation of UDP-GlcNAc (Wellen et al. 2010). Interestingly, IL-3 receptor activates glutamine transporters and thus glucose and glutamine metabolism can be directly coordinated in interleukin-3-dependent cells (Wellen et al. 2010).

Functional relevance of PTMs for metabolic enzyme activities and abundance

Almost any enzyme in central metabolism is subject to a PTM. However, the functional relevance of many of these modifications is not yet clear. One reason for the huge difference between identified and functionally verified posttranslational modifications is the high-throughput capacity in mass spectrometry-based measurements of PTMs and the time-consuming assays to prove their functional relevance. Yet, even when only considering the up-to-date identified PTMs with functional relevance (Figure 4), a considerable number of metabolic enzymes are subject to multiple PTMs. For example, 30% of acetylation sites in human cells are also ubiquitination sites, leading to a competition between acetylation and ubiquitination to regulate protein stability (Wagner et al. 2011). Thus, the question arises how crosstalks between these different modes of regulation are coordinated in a cell. Consequently, the next question is how the cell responds to multiple signals with opposing regulatory consequences. Both questions are largely unexplored, yet the integration of all the regulatory layers results in a highly flexible system, which is of prime importance for metabolic homeostasis.

One example for such an interlayered and integrated response is fatty acid biosynthesis in response to high AcCoA levels (Figure 5). AcCoA availability has been shown to be a major determinant of acetylation events (Lee et al. 2014). Thus, increased AcCoA levels can lead to increased acetylation and thus inhibition of AcCoA synthetase (Hallows et al. 2006; Schwer et al. 2006) -which converts acetate into AcCoA- to prevent further production of AcCoA. Then, the AcCoA-driven acetylation and inhibition of the TCA cycle enzymes isocitrate dehydrogenase (Schlicker et al. 2008; Yu et al. 2012) and succinate dehydrogenase (Cimen et al. 2010) can promote citrate production, which subsequently can then be used for mitochondrial export and fatty acid synthesis rather than for conversion in the TCA cycle. Overall, this can lead to increased citrate levels, which are known to activate AcCoA carboxylase, the enzyme that catalyzes the production of malonyl-CoA, a critical step for fatty acid synthesis (summarized in (Michal and Schomburg 2013)). Yet, before malonyl-CoA can be produced, citrate needs to be cleaved into AcCoA and oxaloacetate by ATP citrate lyase. Strikingly, ATP citrate lyase is also activated by acetylation (Lin et al. 2013). Finally, AcCoA is also known to

activate mTORC1 signaling via an acetylation-dependent mechanism (Marino et al. 2014). One target of mTORC1 is the transcription factor SREBP-1 (Porstmann et al. 2008), which is a known activator of gene transcription involved in fatty acid synthesis (Yokoyama et al. 1993). Thus, increased AcCoA concentration can promote its own conversion into fatty acids.

In conclusion, PTMs constitute a central mechanism by which the cells can sense metabolic levels, allowing feedback regulation from metabolism not only to signaling pathways and gene expression but also to itself. While little is known about the hierarchy and interdependence of PTMs for metabolic auto-regulation, the complexity of this tight regulation contributes to the multi-causality of numerous diseases and particularly cancer.

CONCLUSION

Fine-tuned homeostasis of metabolism is achieved by a bi-directional interplay between metabolism with signaling and transcription factors, metabolic auto-regulation, and posttranslational as well as epigenetic modifications. Many of these regulatory patterns have been established, and new links are constantly discovered. Thus, the arising questions to answer are: What is the hierarchical layer between the different regulatory links? What determines the cellular response when opposite signals are received? How can specific metabolic processes be rationally controlled without global cellular responses? Answering these questions will contribute to the development of novel strategies to target the aberrant metabolism in diseased cells without severe side effects by specifically manipulating the complex interplay of the cell-embedded regulatory mechanisms that sustain homeostasis in healthy cells.

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflict of interest.

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FIGURE LEGENDS

Figure 1: **Feedback regulation of metabolism to itself and to signaling pathways.** Black arrows represent the feedback from metabolism to itself and to signaling pathways, blue dots the level of regulation of this feedback, and grey arrow the feedback from signaling to metabolism.

Figure 2: **Network of the metabolic feedback to signaling pathways.** AMPK, p53 and mTOR are three major regulators of cellular metabolism and their activities are interdependent. Metabolites are represented in blue, proteins in green and signaling regulators in black. Blue arrows represent the feedback from metabolites to signaling regulators, green arrows the feedback from metabolic enzymes to signaling regulators, black arrows the interdependent feedback between cell signaling regulators, and the dashed arrow represents the feedback from amino acids to amino acid sensing proteins.

Abbreviations: AcCoA: acetyl-CoA; AMP: adenosine monophosphate; AMPK: AMP-activated protein kinase; ATP: adenosine triphosphate; FH: fumarate hydratase; HK2: hexokinase 2; MDH1: malate dehydrogenase 1; ME1: malic enzyme 1; ME2: malic enzyme 2; mTORC1: mammalian target of rapamycin complex 1; mTORC2: mammalian target of rapamycin complex 2; n-3 PUFA: n-3 polyunsaturated fatty acids; NAD^+: nicotinamide adenine dinucleotide $NADP^+$: nicotinamide adenine dinucleotide phosphate; NADPH: reduced $NADP^+$; NO: nitric oxide; RNS: reactive nitrogen species; ROS: reactive oxygen species..

Figure 3: **Novel metabolic regulation of central metabolism.** Metabolic pathways of central carbon metabolism are indicated with black arrows. Main metabolites that are involved as trigger or target of metabolic regulation of metabolism are depicted in blue and proteins in green. Blue and green arrows indicate regulation from metabolites or enzymes, respectively.

*NO inhibits the $NADP^+$-dependent isocitrate dehydrogenase and aconitase.

Abbreviations: 6PGD: 6-phosphogluconate dehydrogenase; ETC: electron transport chain; NO: nitric oxide; palm-CoA: palmitoyl-CoA; PDH: pyruvate dehydrogenase; PhGDH: phosphoglycerate dehydrogenase; PKM1/PKM2: pyruvate kinase 1 and 2; ROS: reactive oxygen species; SUCNR: succinate receptor.

Figure 4: **Posttranslational modifications (PTMs) of metabolic enzymes**. Most PTMs are dependent on metabolite levels, and in turn regulate the activity or abundance of metabolic enzymes. Only PTMs of metabolic enzymes that were functionally verified are represented. Acetylation modifications are depicted as blue dots, phosphorylation as green dots, ADP-ribosylation as purple dots, succination as yellow dots, succinylation as red dots, glutathionylation as grey dots, ubiquitination as orange dots, carbonylation as brown dots. Enzymes are marked in green.

Abbreviations: 6PGD: 6-phosphogluconate dehydrogenase (Shan et al. 2014); ACC: AcCoA carboxylase (Kim et al. 1989; Chen et al. 2000; Park et al. 2002; Qi et al. 2006; O'Neill et al. 2014); ACL: ATP citrate lyase (Pierce et al. 1981; Wagner and Vu 1995; Potapova et al. 2000; Migita et al. 2008; Lin et al. 2013); ACO: aconitase (Yan et al. 1997; Han et al. 2005; Liu et al. 2013; Ternette et al. 2013); ACS: AcCoA synthetase (Hallows et al. 2006; Schwer et al. 2006); ASL: argininosuccinate lyase

(Zhao et al. 2010); CAD: carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (Ben-Sahra et al. 2013; Robitaille et al. 2013); CPS: carbamoyl phosphate synthase 1 (Nakagawa et al. 2009; Du et al. 2011);; EHHADH: enoyl-CoA hydratase / 3-hydroxyacyl CoA dehydrogenase (Zhao et al. 2010); ENO: enolase (Fratelli et al. 2002; Reed et al. 2009; Lii et al. 2011); ETC: electron transport chain (Ahn et al. 2008; Hurd et al. 2008; Garcia et al. 2010; Padrao et al. 2011; Wang et al. 2011; Ryan et al. 2012; Acin-Perez et al. 2014); FH: fumarate hydratase (Klaus et al. 2012); G6PD: glucose-6-phosphate dehydrogenase (Zhang et al. 2000; Xu et al. 2005; Wang et al. 2014); GAPDH: glyceraldehyde-3-phosphate dehydrogenase (Dimmeler et al. 1992; Molina y Vedia et al. 1992; Zhang and Snyder 1992; Lind et al. 1998; Tisdale 2002; Cahuana et al. 2004; Blatnik et al. 2008; Ventura et al. 2010); GDH: glutamate dehydrogenase (Herrero-Yraola et al. 2001; Haigis et al. 2006; Schlicker et al. 2008)); GLS: glutaminase (Colombo et al. 2011); GS: glutamine synthetase (Moss et al. 1984; Gorg et al. 2007); HK: hexokinase (Roberts and Miyamoto 2015); IDH: isocitrate dehydrogenase (Schlicker et al. 2008; Zhang et al. 2011; Yu et al. 2012); KGDH: alpha-ketoglutarate dehydrogenase (Humphries and Szweda 1998; Humphries et al. 1998; Applegate et al. 2008); LCAD: long-chain AcCoA dehydrogenase (Ahn et al. 2008); LDH : lactate dehydrogenase (Holbrook and Ingram 1973; Onishi et al. 2005; Fan et al. 2011; Avezov et al. 2014); MCD: Malonyl-CoA Decarboxylase (Laurent et al. 2013); MDH: malate dehydrogenase (Nguyen and Donaldson 2005; Reed et al. 2009; Zhao et al. 2010; Kim et al. 2013a); PDH: pyruvate dehydrogenase (Linn et al. 1969; Humphries and Szweda 1998; Han et al. 2008; Jing et al. 2013; Park et al. 2013; Ozden et al. 2014); PGAM: phosphoglycerate mutase (Lo and Hannink 2006; Vander Heiden et al. 2010; Hallows et al. 2012; Hitosugi et al. 2013; Tsusaka et al. 2014; Xu et al. 2014b); PFK1: phosphofructo kinase-1 (Kagimoto and Uyeda 1979; Yi et al. 2012); PFK2: Phosphofructokinase-2/Fructose-2,6-bisphosphatase (Rosa et al. 1995; Seo and Lee 2014); PKM2: pyruvate kinase isoform M2 (Hitosugi et al. 2009; Yang et al. 2012; Lv et al. 2013); OTC: ornithine transcarbamylase (Hallows et al. 2011); PEPCK : phosphoenolpyruvate carboxykinase (Jiang et al. 2011; Yang et al. 2012); SDH: succinate dehydrogenase (Chen et al. 2007; Cimen et al. 2010; Park et al. 2013); TPI: triosephosphate isomerase (Lee et al. 2010; Huang et al. 2012).

Figure 5: **Acetyl-coA (AcCoA) can control its own conversion to fatty acids through a multilayered feedback regulation to signaling pathways and metabolic enzymes.** Black lines represent the metabolic pathways leading to biosynthesis of fatty acids, red lines indicate inhibition and blue lines indicate activation.

Abbreviations: mTORC1: mammalian target of rapamycin complex 1, SREBP-1: sterol regulatory element-binding protein 1

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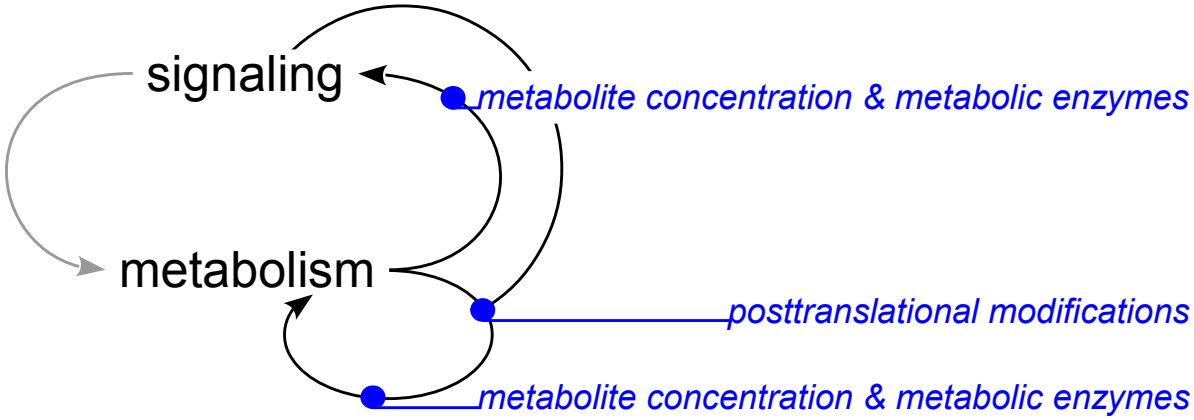
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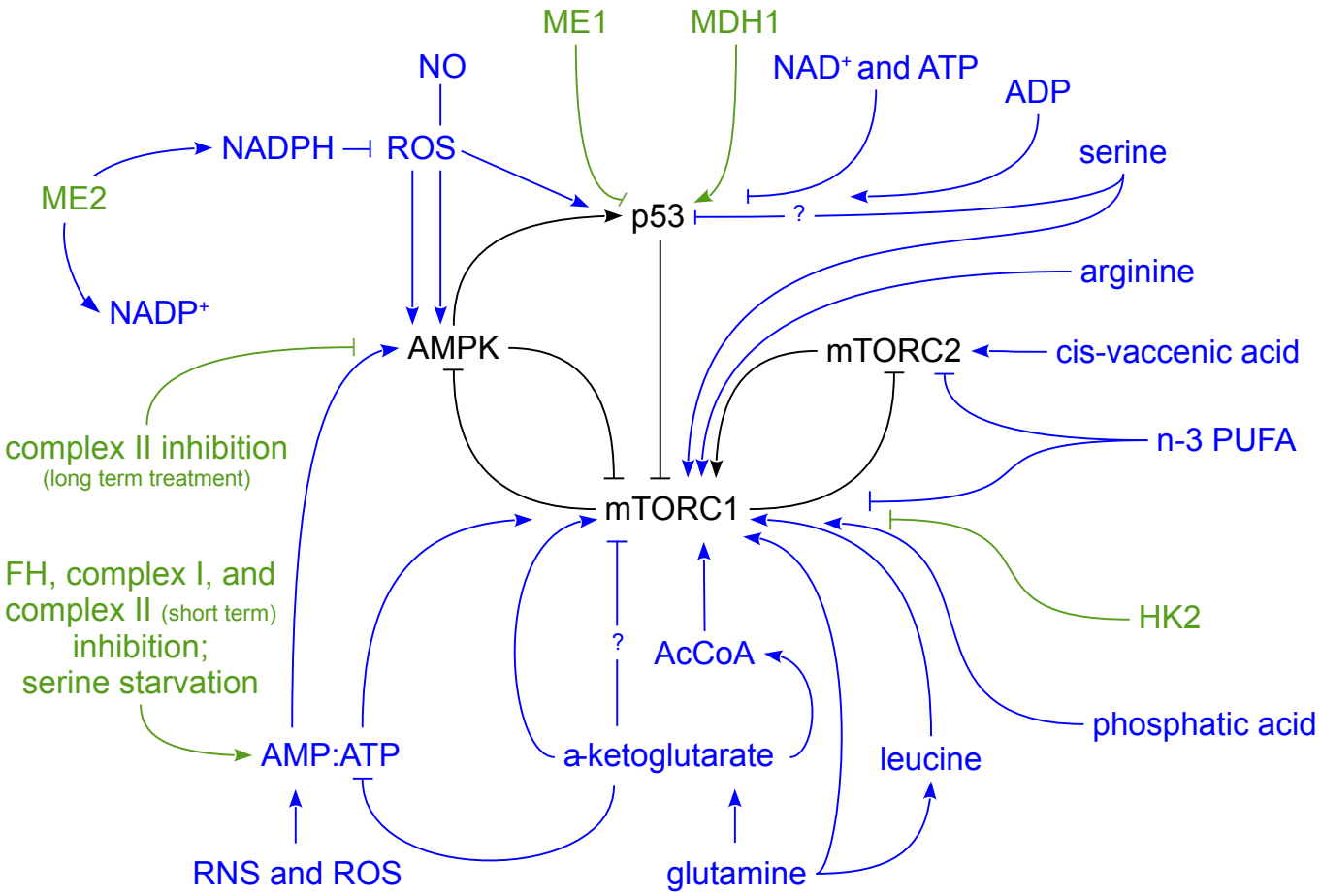
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p53
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mTORC2
cis-vaccenic acid
complex II inhibition
(long term treatment)
n-3 PUFA
mTORC1
FH, complex I, and
complex II (short term)
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serine starvation
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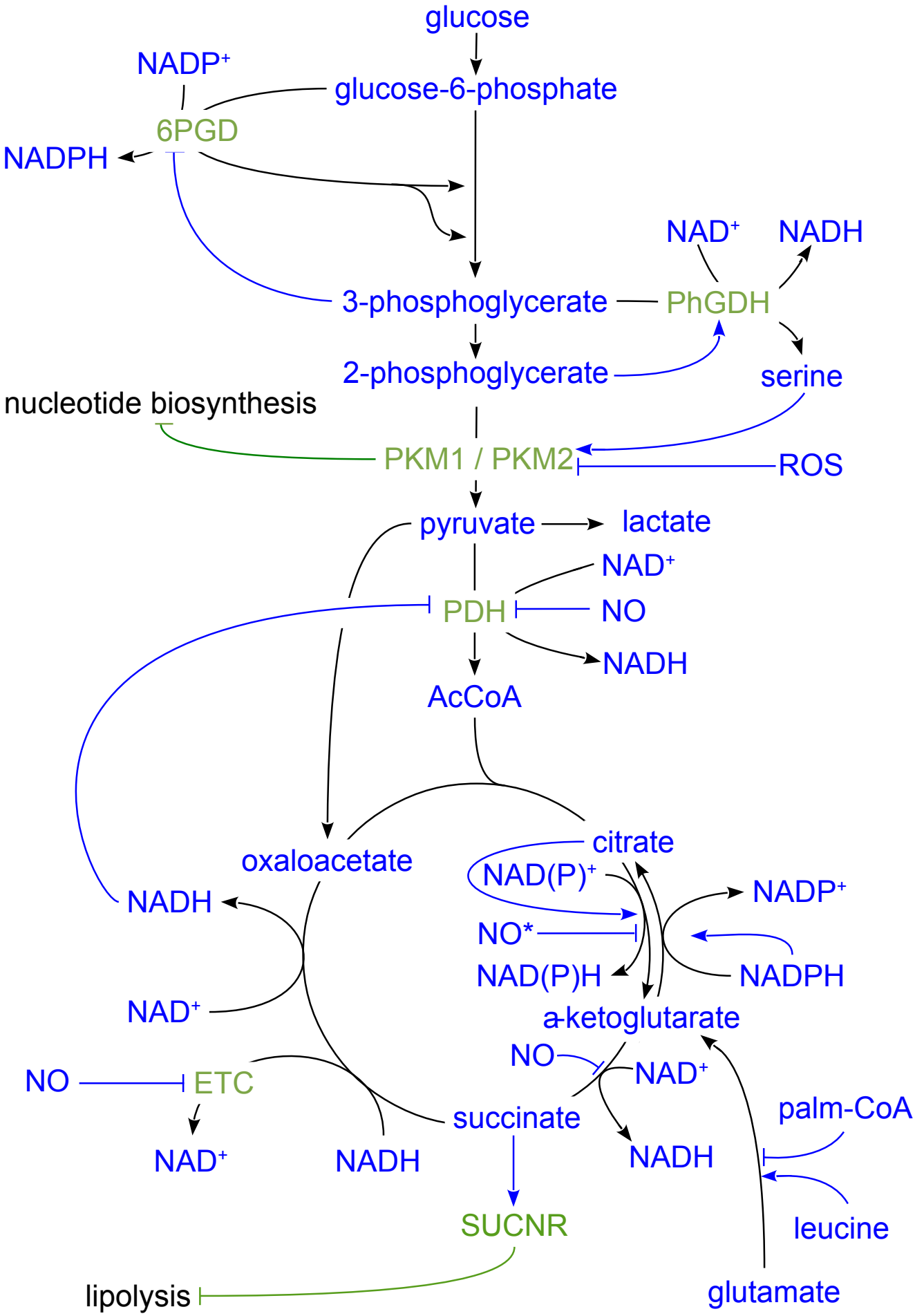
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nucleotide biosynthesis
PKM1 / PKM2
ROS
pyruvate
lactate
NAD+
PDH
NO
NADH
AcCoA
oxaloacetate
citrate
NADH
NAD(P)+
NADP+
NO*
NAD(P)H
NADPH
NAD+
a-ketoglutarate
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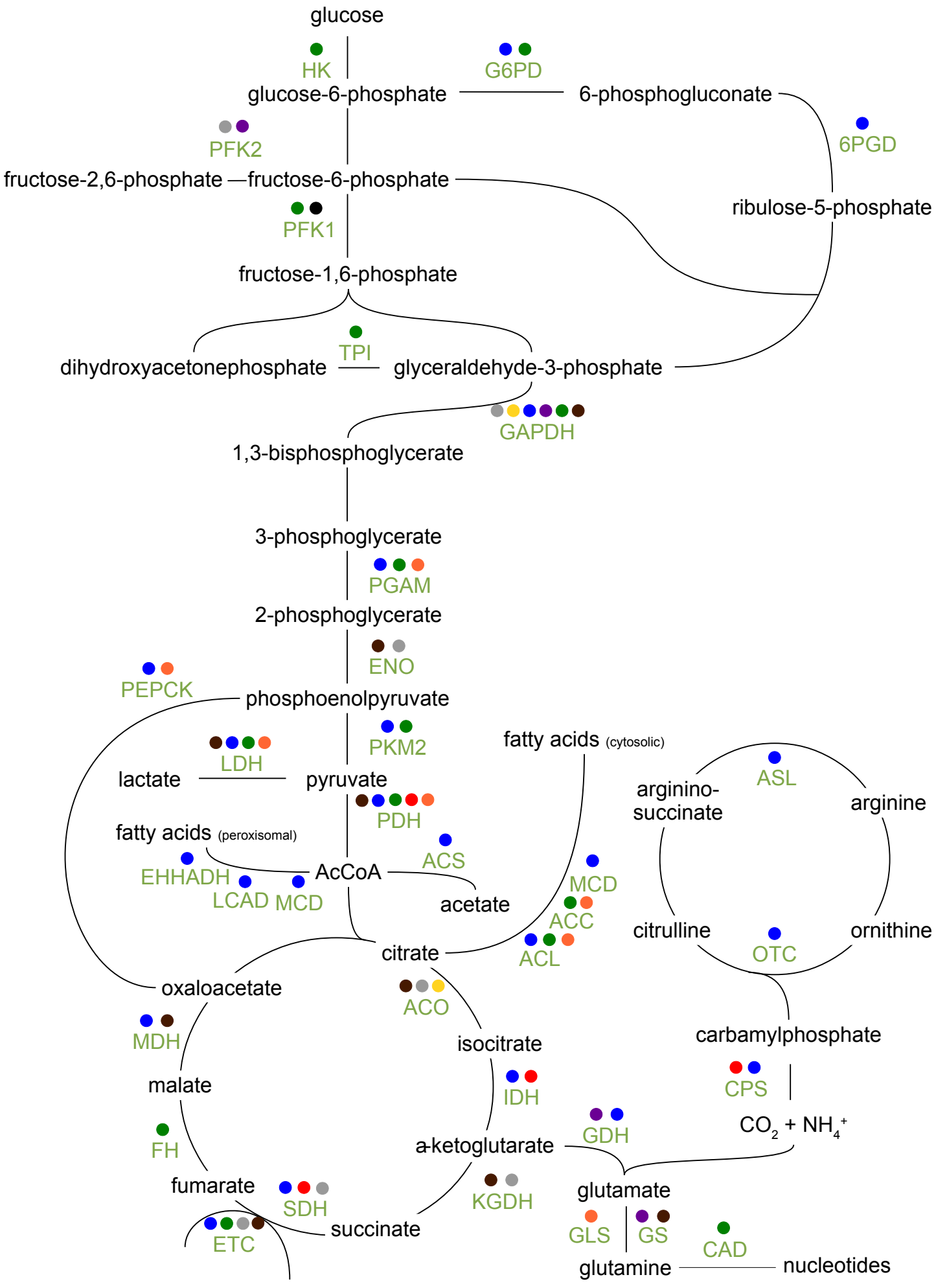
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PFK1
fructose-1,6-phosphate
TPI
dihydroxyacetonephosphate
glyceraldehyde-3-phosphate
GAPDH
1,3-bisphosphoglycerate
3-phosphoglycerate
PGAM
2-phosphoglycerate
ENO
PEPCK
phosphoenolpyruvate
PKM2
LDH
lactate
pyruvate
PDH
fatty acids (cytosolic)
fatty acids (peroxisomal)
ACS
EHHADH
LCAD
MCD
AcCoA
acetate
MCD
ACC
ACL
citrate
ASL
arginino-
succinate
arginine
citrulline
OTC
ornithine
oxaloacetate
ACO
MDH
isocitrate
carbamylphosphate
CPS
malate
IDH
GDH
CO2 + NH4+
FH
a-ketoglutarate
fumarate
SDH
KGDH
glutamate
succinate
ETC
GLS
GS
CAD
glutamine
nucleotides
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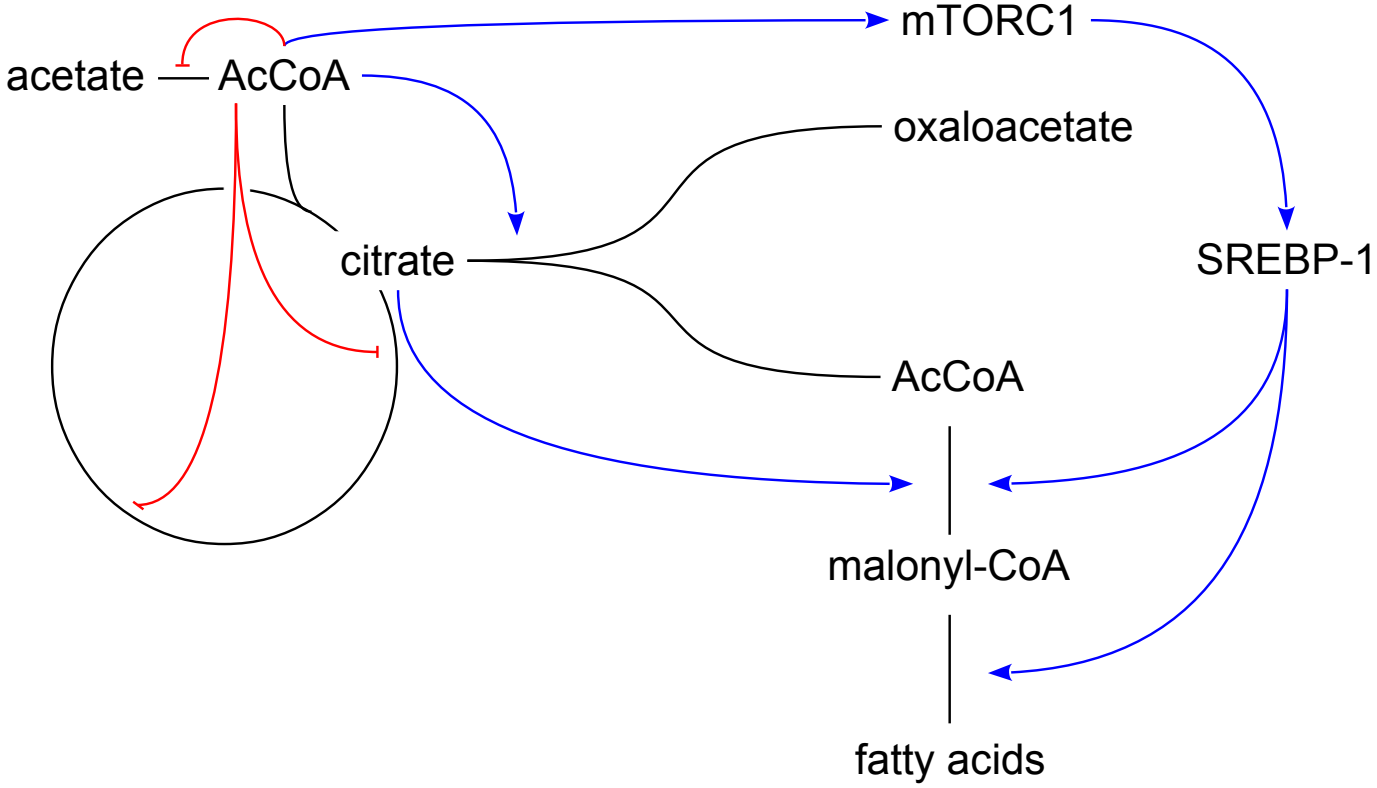
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